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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/444,067	11/19/99	MURPHY B	17634-000512

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EXAMINER	
BRUMBACK, B	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/444,067	Applicant(s) Murphy et al.
	Examiner Brenda Brumback	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 15, 2000*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *63-78, 88-122, 128-145, and 147-161* is/are pending in the application.

4a) Of the above, claim(s) *68-78, 88, 90-92, 96-119, 137-145, 147, 149, 15*: is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *63-67, 89, 93-95, 120-122, 128-136, 148, 150, and 160* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 11

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group I, claims 63-69, 88-95, 108-114, 119-122, 128-138, 147-150, and 156-161 and species 3 (recombinant RSV with a SH gene deletion) in Paper No. 14 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Pending claims are 63-78, 88-122, 128-145, and 147-161. Claims 70-78, 96-107, 115-118, 139-145, and 151-155 are withdrawn from consideration as drawn to a nonelected invention. Claims 68, 69, 88, 90-92, 108-114, 119, 137, 138, 147, 149, 156-159, and 161 are withdrawn from consideration as directed to a nonelected species. Claims 63-67, 89, 93-95, 120-122, 128-136, 148, 150, and 160 are under examination to the extent that they read on the elected species, recombinant RSV with a SH gene deletion.

Information Disclosure Statement

3. The Information Disclosure Statements filed 07/27/2000 and 12/08/2000 have been entered as Papers # 7 and 11 respectively. A signed copy of Paper # 11 is attached hereto. Paper

7 has not yet been considered, as the parent file containing the references (U.S. Application No. 08/892,403) is not presently available. The IDS will be considered with the next Office action.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claim 131 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 23, 24, and 62 of copending Application No. 09/291,894. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to recombinant RSV comprising RSV with sequences of different human subgroups (A and B) and an SH gene deletion.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

3. Claim 120 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Claim 120 recites the recombinant RSV(respiratory syncytial virus) of claim 63, which is a virus. Since claim 63 is drawn to a virus, claim 120 does not further limit the independent claim.

Claim Rejections - 35 USC § 112

4. Claims 128-131 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the

art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to a vaccine to induce protection against RSV comprising recombinant RSV with a partial or complete (SH) gene deletion. As such, the claims encompass administration of the claimed vaccine in order to induce protection against subsequent RSV infection in humans.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that RSV vaccines comprising live attenuated virus often do not confer protection against subsequent RSV infection due to factors such as maternally acquired serum antibodies,

incomplete immunity, and the existence of multiple antigenically diverse strains (see Murphy et al., Virus Research 32:13-36, 1994, especially pages 14-15 and page 22, last partial paragraph, through page 26, first paragraph).

The amount of direction or guidance present and the presence or absence of working examples: The disclosure teaches how to make recombinant RSV having a deletion of the SH gene (see Example XIII beginning at page 161) and how to elicit an immunogenic response in BALB/c mice by administration of the mutant RSV. However, the disclosure does not teach that the immunogenic response is protective in humans against subsequent RSV infection in the presence of passively acquired maternal antibodies or that it is protective against multiple strains of human RSV.

The breadth of the claims and the quantity of experimentation needed: Because the claims are drawn to vaccine compositions for protection against RSV in humans and because the art teaches that attenuated RSV vaccines are not protective against all subsequent RSV infections, it would require undue experimentation by one of skill in the art to be able to practice the claimed invention.

5. Claim 121 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 121 is drawn to a subviral particle; however, claims 121 depends from claim

63 which recites a virus. The term "virus" denotes a complete virion. It is therefore unclear how a complete virion or virus can also be a subviral particle, making the claim indefinite.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

a. Claims 63-67, 89, 93-95, 120, 121, 128, 131-136, 148, and 150 are rejected under 35 U.S.C. 103(a) as being unpatentable over Collins et al. (Proc. Natl. hAcad. Sci USA, 92:11563-11567, Dec. 1995).

The claimed invention is drawn to an isolated infectious recombinant respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, and an RNA polymerase elongation factor, wherein a modification is introduced within the genome or antigenome comprising a partial or complete (SH) gene deletion and wherein the recombinant RSV is further modified by one or more (two to three) attenuating mutations adopted from different biologically derived mutant RSV strains or stabilized by multiple nucleotide changes in the codon specifying the mutation. The claimed invention is

also drawn to immunogenic compositions comprising the recombinant RSV virus for eliciting an immune response against both RSV subgroups A and B, and to isolated polynucleotides comprising the modified recombinant RSV genome or antigenome.

Collins teaches infectious recombinant RSV comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, and an RNA polymerase elongation factor, wherein defined changes can be introduced for development of live attenuated vaccine strains (see the abstract). Collins suggests that deletion or modification of specific genes, such as the SH gene, may result in attenuated RSV strains with enhanced immunogenicity and a higher level of protection against RSV infection than wild-type virus. Collins teaches that combining an RSV subgroup B gene with the RSV A genome broadens the immune response to cover a wider spectrum of diverse RSV strains in the population (see page 11566, the paragraph bridging columns 1 and 2 and page 11567, paragraph). Finally, Collins teaches biologically derived mutant RSV strains which are stabilized by two or more additional nucleotides and amino acid substitutions (see [age 11566, column 2, first full paragraph). One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have made a recombinant attenuated RSV comprising a partial or complete (SH) gene deletion, incorporating genes from RSV subgroups A and B, further modified by one or more attenuating mutations adopted from biologically derived mutant RSV strains, and stabilized by multiple nucleotide changes in the codon specifying the mutation, according to the teachings of Collins. One of

ordinary skill in the art at the time the invention was made would have been motivated to do so in order to make a vaccine strain with enhanced immunogenicity, as is suggested by Collins.

b. Claims 122, 129, and 130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Collins et al. in view of Randolph et al. (EPA 0 567 100).

The claimed invention is drawn to an isolated infectious recombinant respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, and an RNA polymerase elongation factor, wherein a modification is introduced within the genome or antigenome comprising a partial or complete (SH) gene deletion formulated in a dose of 10^3 to 10^6 PFU of attenuated virus for administration to the upper respiratory tract by spray, droplet or aerosol.

As was set forth above, Collins et al. teach an isolated infectious recombinant respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, and an RNA polymerase elongation factor, and suggest modifying the genome or antigenome by a partial or complete (SH) gene deletion for a vaccine composition with enhanced immunogenicity. Collins et al. do not teach formulation of the immunogenic dose or preferred route of administration.

Randolph et al. teach intranasal administration of an aerosol containing 10^6 PFU of attenuated infectious RSV for eliciting systemic immunity (see page 3, lines 1-4; page 6, lines 1-10; and page 47, Table 19).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have administered the recombinant RSV taught by Collins et al. via the dosage and route taught by Randolph because Randolph teaches that the dose and method are effective for eliciting systemic immunity to RSV infection.

c. Claim 160 is rejected under 35 U.S.C. 103(a) as being unpatentable over Collins et al. in view of Klein et al. (WO 93/14207; of record in Paper # 11).

The claimed invention is drawn to an isolated infectious recombinant respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, and an RNA polymerase elongation factor comprising a partial or complete (SH) gene deletion and incorporating a gene or gene segment from parainfluenza virus (PIV).

As was outlined previously, Collins et al. teach an isolated infectious recombinant respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, and an RNA polymerase elongation factor, and suggest modifying the genome or antigenome by a partial or complete (SH) gene deletion for a vaccine composition with enhanced immunogenicity. Collins et al. further teach that one or more genes of the subgroup B genome can be incorporated into the subgroup A genome, and suggest that genes from other respiratory pathogens might be incorporated into the RSV genome,

as well (see page 11567, second to last sentence of the page). Collins et al. do not specifically teach incorporation of a gene or gene segment from PIV into recombinant RSV.

Klein et al. teach multimeric hybrid genes comprising gene sequences from RSV and PIV. Klein et al. teach that the hybrid recombinant antigen encoded by the hybrid genes is capable of protecting infants and other susceptible individuals against both RSV and PIV (see the abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated a PIV gene or gene segment into the infectious recombinant RSV taught by Collins et al. in order to elicit an immunogenic response against both pathogens by administration of a single virus.

Conclusion

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1642 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a

Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

BB
May 2, 2001

Brenda Brumback,
Patent Examiner